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- (71) Applicant (for all designated States except US): **MEDINOX, INC.** [US/US]; Suite 201, 11575 Sorrento Valley Road, San Diego, CA 92121 (US).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): **LAI, Ching-San** [US/US]; 209 Lolita Street, Encinitas, CA 92024 (US). **VASSILEV, Vassil** [BG/US]; Apartment 1918, 7588 Charmant Drive, San Diego, CA 92122 (US).
- (74) Agent: **REITER, Stephen, E.**; Gray Cary Ware & Freidenrich LLP, Suite 1600, 4365 Executive Drive, San Diego, CA 92121 (US).
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WO 99/66918 A1

(54) Title: **THERAPEUTIC METHODS EMPLOYING DISULFIDE DERIVATIVES OF DITHIOCARBAMATES AND COMPOSITIONS USEFUL THEREFOR**

(57) Abstract: The present invention provides a novel dithiocarbamate disulfide dimer useful in various therapeutic treatments, either alone or in combination with other active agents. In one method, the disulfide derivative of a dithiocarbamate is coadministered with an agent that inactivates (or inhibits the production of) species that induce the expression of nitric oxide synthase to reduce the production of such species, while, at the same time reducing nitric oxide levels in the subject. In another embodiment, free iron ion levels are reduced in a subject by administration of a disulfide derivative of a dithiocarbamate(s) to scavenge free iron ions, for example, in subjects undergoing anthracycline chemotherapy. In another embodiment, cyanide levels are reduced in a subject by administration of a disulfide derivative of a dithiocarbamate so as to bind cyanide in the subject. In a further aspect, the present invention relates to compositions and formulations useful in such therapeutic methods.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/14237

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A61K 31/105

US CL :514/707, 810, 824, 826, 866, 870, 885, 895, 921, 925

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/707, 810, 824, 826, 866, 870, 885, 895, 921, 925

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
APS, STN, CAS-ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,206,264 A (MARANGOS) 27 April 1993, see entire document.	1-7, 9-24, 29-39, 46 and 47
X	US 5,373,021 A (MARANGOS) 13 December 1994, see entire document.	1-7, 9-24, 29-39, 46 and 47
X,P	US 5,877,203 A (MEDFORD et al.) 02 March 1999, see entire document.	1-7,9-24, 29-39, 46 and 47

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
B earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*&* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

22 JANUARY 2001

Date of mailing of the international search report

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Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer
Dorothy Lawrence For
KEVIN E. WEDDINGTON

Telephone No. (703) 308-0196

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/14237

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
1-7, 9-24, 29-39, 46 and 47
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/14237

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

Group I, Claim(s) 1-5, 29-36, 39 and 47 are drawn to a composition and a method for the in vivo reduction of free iron levels in a subject with a composition comprising bis(dithiocarbamate) and a carrier.

Group II, Claim(s) 1-5, 37, 38 and 47 are drawn to a composition and methods for treating a subject having elevated circulating levels and overproduction of free iron ions.

Group III, Claim(s) 1-5, 40-45 and 47 are drawn to a composition and a method for the in vivo reduction of cyanide levels in a subject.

Group IV, Claim(s) 1-5 and 46 are drawn to a composition and a method for the treating a disease associated with a nuclear actor Kappa B pathway.

Group V, Claim(s) 1-7, 9-24 and 47 are drawn to a composition and a method for the in vivo reduction of nitric oxide levels in a subject.

Group VI, Claim(s) 8 is drawn to a method for directly or indirectly treating the production of species with a composition comprising one agent capable of directly or indirectly inactivating and one disulfide dithiocarbamate.

Group VII, Claim(s) 25 and 26 are drawn to a therapeutic process containing a combination of a therapeutic agent and a nitric oxide scavenger.

Group VIII, Claim(s) 27 and 28 are drawn to a composition comprising a carrier, an agent capable of inactivating materials, and a nitric oxide scavenger.

The inventions listed as Groups I-VIII do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The eight inventions are independent and distinct, each from the other as they have acquired a separate status in the art as shown by their separate matter for inventive effort because a method for the reduction of nitric oxide levels in a patient is different from a method for the reduction of cyanide levels in a patient since both methods depend on the patient in need of such treatment for each individual condition. Group I is completely different from Group VIII because of different components used to make the instant compositions in each invention.